INTRODUCTION
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BASIC SCIENCE


A method using gas chromatography-mass spectrometry (GC-MS) and solid-phase extraction (SPE) was developed for the determination of ajulemic acid (AJA), a non-psychoactive synthetic cannabinoid with interesting therapeutic potential, in human plasma. When using two calibration graphs, the assay linearity ranged from 10 to 750ng/ml, and 750 to 3000ng/ml AJA. The intra- and inter-day precision (R.S.D., %), assessed across the linear ranges of the assay, was between 1.5 and 7.0, and 3.6 and 7.9, respectively. The limit of quantitation (LOQ) was 10ng/ml. The amount of AJA glucuronide was determined by calculating the difference in the AJA concentration before ("free AJA") and after enzymatic hydrolysis ("total AJA"). The present method was used within a clinical study on 21 patients suffering from neuropathic pain with hyperalgesia and allodynia. For example, plasma levels of 599.4+/-37.2ng/ml (mean+/-R.S.D., n=9) AJA were obtained for samples taken 2h after the administration of an oral dose of 20mg AJA. The mean AJA glucuronide concentration at 2h was 63.8+/-127.9ng/ml.


Cannabinoids, including the bioactive constituents of the marijuana plant, their synthetic analogs, and endogenous lipids with cannabinoid-like activity, produce their biological effects by interacting with specific receptors. To date, two G protein-coupled cannabinoid receptors have been identified by molecular cloning, CB(1) receptors mainly expressed in the brain and mediating most of the neurobehavioral effects of cannabinoids and CB(2) receptors expressed by immune and hematopoietic tissues. Recent findings indicate that some cannabinoid effects are not mediated by either CB(1) or CB(2) receptors, and in some cases there is compelling evidence to implicate additional receptors in these actions. These include transient receptor potential vanilloid 1 (TRPV(1)) receptors and as-yet-unidentified receptors implicated in the endothelium-dependent vasodilator effect of certain cannabinoids and in the presynaptic inhibition of glutamatergic neurotransmission in the hippocampus. The case for these additional receptors is being reviewed here.


The pharmacological and neuroprotective properties of two ester analogs of the endocannabinoids, arachidonoylthymyleglycol (AA-EG) and alpha,alpha-dimethyl arachidonoylthymyleglycol (DMA-EG), were investigated. We examined the interaction of both compounds with cannabinoid receptors (CB(1) and CB(2)) and their efficacy in functional assays. In competition binding assays, AA-EG and DMA-EG had low potency to displace the CB(1)/CB(2) agonist [(3)H]CP-55,940 in membrane preparations expressing rodent or human receptors.
Binding data correlate with low efficacy of both compounds as regards to inhibition of adenylyl cyclase activity. It was also shown that DMA-EG resists hydrolysis by rat brain membranes while AA-EG undergo complete splitting under these conditions. In the cannabinoid tetrad, AA-EG induced hypomotility, analgesia, catalepsy and decreased rectal temperature indicating cannabimimetic activity. By contrast, DMA-EG was completely inactive in the same models. DMA-EG and AA-EG potently protected rat cortical neurons in culture against oxygen deprivation at nanomolar concentrations. In glutamate-induced damage, the compounds were less active protecting neurons at micromolar concentrations. The data obtained indicate that the ester endocannabinoid template can be used for the development of new compounds with potent biological activity lacking some of the undesirable behavioral side effects.


Abstract Cannabinoids are widely abused drugs. Here we show that chronic administration of Delta(9)-tetrahydrocannabinol (Delta(9)-THC), the active psychotropic agent in marijuana and hashish, at 1.5 mg per kg per day intraperitoneally for 7 days, increases the expression, at both mRNA and protein levels, of brain-derived neurotrophic factor (BDNF), in specific rat brain areas, notably in those involved in reward and addiction. Real-time PCR revealed a 10-fold up-regulation of BDNF mRNA in the nucleus accumbens (Nac) upon chronic Delta(9)-THC treatment, but there was no change at 3 or 24 h after a single injection. Smaller increases in mRNA levels were found in the ventral tegmental area (VTA), medial prefrontal cortex and paraventricular nucleus (PVN). Immunohistochemistry showed large increases in BDNF-stained cells in the Nac (5.5-fold), posterior VTA (4-fold) and PVN (1.7-fold), but no change was observed in the anterior VTA, hippocampus or dorsal striatum. Altogether, our study indicates that chronic exposure to Delta(9)-THC up-regulates BDNF in specific brain areas involved with reward, and provides evidence for different BDNF expression in the anterior and posterior VTA. Moreover, BDNF is known to modulate synaptic plasticity and adaptive processes underlying learning and memory, leading to long-term functional and structural modification of synaptic connections. We suggest that Delta(9)-THC up-regulation of BDNF expression has an important role in inducing the neuroadaptive processes taking place upon exposure to cannabinoids.


Abstract The endocannabinoid system is involved in a variety of effects of drugs of misuse, and blockade of the cannabinoid CB1 receptor by selective antagonists elicits marked reductions in the role of the cannabinoid CB1 receptor in the modulation of alcohol misuse vulnerability in rats. Accordingly, using nonelected Wistar rats and genetically selected Marchigian Sardinian alcohol-preferring (msP) rats, we investigated the effect of the CB1 antagonist SR141716A on operant alcohol self-administration and on reinstatement of alcohol-seeking behavior by environmental conditioning factors. In addition, in situ hybridization studies in both strains were performed to measure cannabinoid CB1 receptor mRNA in different brain areas of these animals. Results showed that intraperitoneal administration of SR141716A (0.03, 1.0 and 3.0 mg/kg) markedly inhibits ethanol self-administration and conditioned reinstatement of alcohol-seeking behavior in both strains of rats. ED50 analysis showed significantly higher sensitivity (P < 0.05) to the effect of SR141716A in msP rats than in heterogeneous Wistar rats. In situ hybridization studies revealed that, compared with Wistar rats, msP animals have consistently greater cannabinoid CB1 receptor mRNA expression in a number of brain areas, including the frontoparietal cortex, caudate-putamen and hippocampus (CA1 and dentate gyrus areas). In conclusion, we provide clear evidence that blockade of CB1 receptors reduces both ethanol self-administration and conditioned reinstatement of alcohol-seeking behavior in rats. In addition, current pharmacological and neuroanatomical data suggest that an altered function of the CB1 receptor system exists between genetically selected alcohol-preferring msP rats and a heterogeneous animal population.

Following the discovery of two CB1 genes in the fish Fugu rubripes, investigations on the phylogeny of endocannabinoids have indicated that this system is highly conserved. Our study demonstrated that CB1 receptors are expressed in the CNS and gonads of two teleosts, Carassius auratus and Pelvicachromis pulcher, and they show a high percentage of sequence identity with Fugu rubripes CB(1A) and Danio rerio CB1. By means of immunohistochemistry for CB1, sGnRH, and TH, we found a codistribution of these signaling molecules in the basal telencephalon/preoptic area, which are key centers for gonadotropic regulation. We therefore suggest that endocannabinoids are possibly involved in modulating fish reproduction at both the central and peripheral levels.


The present study shows that the selective cannabinoid CB1 receptor antagonist SR141716A attenuated responding for both nicotine- and sucrose-associated stimuli in a long-term extinction-reinstatement model. The results suggest that endocannabinoids play a general role in modulating cue reactivity or conditioned reinforcement following prolonged abstinence of both drug and natural reinforcers. In line with previous preclinical and recent clinical observations, our results provide a strong rationale for the use of CB1 antagonists in the treatment of addictive behaviors.


Cannabinoi CB1-receptor stimulation in DDT(1) MF-2 smooth muscle cells induces a rise in [Ca(2+)](i), which is dependent on extracellular Ca(2+) and modulated by thapsigargin-sensitive stores, suggesting capacitative Ca(2+) entry (CCE), and by MAP kinase. Non-capacitative Ca(2+) entry (NCCE) stimulated by arachidonic acid (AA) partly mediates histamine H(1)-receptor-evoked increases in [Ca(2+)](i) in DDT(1) MF-2 cells. In the current study, both Ca(2+) entry mechanisms and a possible link between MAP kinase activation and increasing [Ca(2+)](i) were investigated. In the whole-cell patch clamp configuration, the CB-receptor agonist CP 55,940 evoked a transient, Ca(2+)-dependent K(+) current, which was not blocked by the inhibitors of CCE, 2-APB, and SKF 96365. AA, but not its metabolites, evoked a transient outward current and inhibited the response to CP 55,940 in a concentration-dependent manner. CP 55,940 induced a concentration-dependent release of AA, which was inhibited by the CB(1) antagonist SR 141716. The non-selective Ca(2+) channel blockers La(3+) and Gd(3+) inhibited the CP 55,940-induced current at concentrations that had no effect on thapsigargin-evoked CCE. La(3+) also inhibited the AA-induced current. CP 55,940-induced AA release was abolished by Gd(3+) and by phospholipase A(2) inhibition using quinacrine; this compound also inhibited the outward current. The CP 55,940-induced AA release was strongly reduced by the MAP kinase inhibitor PD 98059. The data suggest that in DDT(1) MF-2 cells, AA is an integral component of the CB(1) receptor signaling pathway, upstream of NCCE and, via PLA(2), downstream of MAP kinase. (c) 2005 Wiley-Liss, Inc.


Rats with a previous history of heroin self-administration were studied to assess interactions occurring between cannabinoids and opioids in an animal model of reinstatement of heroin-seeking behaviour. Rats were trained to self-administer heroin and after a long-term extinction were primed with one of the following non-contingent non-reinforced drug administrations: saline (or vehicle), heroin, synthetic cannabinoid CB(1) receptor agonists (WIN 55,212-2 or CP 55,940), opioid antagonist (naloxone) or CB(1) antagonist (SR 141716A), alone or in combination. After primings, lever-pressing activity was recorded and compared to those
observed during previous phases of training and extinction. Results of this study showed that (i) priming injections of heroin (0.1 mg/kg) as well as CB(1) agonists WIN 55,212-2 (0.15 or 0.30 mg/kg) and CP 55,940 (0.05 or 0.1 mg/kg) completely restore heroin-seeking behaviour; (ii) primings of naloxone (1 mg/kg) and SR 141716A (0.3 mg/kg) had no effect when administered alone; (iii) heroin-induced reinstatement was fully prevented by pre-treatment with either naloxone or SR 141716A; (iv) pre-treatment with SR 141716A significantly reduced WIN 55,212-2 and CP 55,940 priming effects. These results suggest that cannabinoid CB(1) receptors play an important role in the mechanisms underlying relapse to heroin-seeking and depict CB(1) antagonists as possible therapeutic agents for use in the prevention of relapse to heroin abuse.


Drugs metabolised by cytochrome P450 (CYP) such as analgesics may induce acute attacks in patients with hepatic porphyrias. In recent years, preclinical and clinical studies have suggested that cannabinoid pharmaceutical preparations may be potentially useful in the treatment of pain. The purpose of the study was to examine the effects of CP-55,940, a cannabinoid CB(1) receptor agonist, on the hepatic heme metabolism in mice. To this end, hepatic activities of aminolevulinic acid synthase (ALAS), heme oxygenase (HO) and CYP levels were determined in mice treated with CP-55,940 (0.5mg/kg/day; i.p.; 5 or 24 days). Results showed that treatment with CP-55,940 decreased CYP concentrations by 80% and increased HO activity by 158%. However, ALAS activity also decreased by 37%, suggesting that regulatory free heme pool was not modified. Our findings indicate that CP-55,940 and its metabolites do not behave as porphyrinogenic drugs and may potentially be safe for treating pain in patients with acute porphyrias.


The globus pallidus receives its major glutamatergic input from the subthalamic nucleus and subthalamic nucleus neurons synthesize CB(1) cannabinoid receptors. The hypothesis of the present work was that CB(1) receptors are localized in terminals of subthalamo-pallidal glutamatergic axons and that their activation leads to presynaptic modulation of neurotransmission between these axons and globus pallidus neurons. Patch-clamp studies were carried out on oblique-sagittal mouse brain slices. The subthalamic nucleus was stimulated electrically and the resulting excitatory postsynaptic currents (EPSCs) were recorded in globus pallidus neurons. The mixed CB(1)/CB(2) receptor agonist R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-be nzoxazin-yl]-(1-naphthalenyl)methanone mesylate (WIN55212-2; 3x10(-7) M) had no effect on EPSCs. WIN55212-2 (10(-5) M) decreased the amplitude of EPSCs by 44+/-8%. The inhibition by WIN55212-2 (10(-5) M) was prevented by the CB(1) antagonist N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole carboxamide (10(-6) M). WIN55212-2 (10(-5) M) did not change the amplitude of spontaneous EPSCs (sEPSCs) recorded in globus pallidus neurons but lowered their frequency. Moreover, WIN55212-2 (10(-5) M) had no effect on currents elicited by direct activation of postsynaptic receptors on globus pallidus neurons by glutamate (10(-3) M) ejected from a pipette. In a final series of experiments, the firing of subthalamic nucleus neurons was recorded; WIN55212-2 (10(-5) M) did not change the firing of these neurons. The results show that activation of CB(1) receptors inhibits glutamatergic neurotransmission between the subthalamic nucleus and the globus pallidus. Lack of effect of cannabinoids on the amplitude of sEPSCs and on currents evoked by direct stimulation of postsynaptic glutamate receptors indicates that the mechanism is presynaptic inhibition of glutamate release from axon terminals. Cannabinoids seem to act preferentially presynaptically: in contrast to their action on axon terminals, they have no effect on somadendritic receptors regulating firing rate. Cannabinoids elicit catalepsy in vivo. The observed inhibition of glutamatergic neurotransmission in the globus pallidus would favor catalepsy.

Delta-9 tetrahydrocannabinol (Delta(9)-THC) and (-)-cannabidiol ((-)-CBD) are major constituents of the Cannabis sativa plant with different pharmacological profiles: (Delta(9)-THC activates cannabinoid CB(1) and CB(2) receptors and induces psychoactive and peripheral effects. (-)-CBD possesses no, or very weak affinity for these receptors. We tested a series of (+)- and (-)-CBD derivatives for central and peripheral effects in mice. None of the (-)-CBD derivatives were centrally active, yet most inhibited intestinal motility. Of the five (+)-CBD derivatives, all with CB(1) receptor affinity, only (+)-7-OH-CBD-DMH (DMH=1,1-dimethylheptyl), acted centrally, while all five arrested defecation. The effects of (+)-CBD-DMH and (+)-7-OH-CBD-DMH were inhibited by the CB(1) receptor antagonist SR141716. The CB(2) receptor antagonist SR144528, and the vanilloid TRPV1 receptor antagonist capsazepine, had no influence. Further, the (-)-CBD derivatives (-)-7-COOH-CBD and (-)-7-COOH-CBD-DMH, displayed antiinflammatory activity. We suggest that (+)-CBD analogues have mixed agonist/antagonist activity in the brain. Second, (-)-CBD analogues which are devoid of cannabinoid receptor affinity but which inhibit intestinal motility, suggest the existence of a non-CB(1), non-CB(2) receptor. Therefore, such analogues should be further developed as antidiarrheal and/or antiinflammatory drugs. We propose to study the therapeutic potential of (-)- and (+)-CBD derivatives for complex conditions such as inflammatory bowel disease and cystic fibrosis.

Gonzalez, S., M. A. Mena, et al. (2005). "Cannabinoid CB(1) receptors in the basal ganglia and motor response to activation or blockade of these receptors in parkin-null mice." Brain Res.

The endocannabinoid transmission becomes overactive in the basal ganglia in Parkinson's disease (PD), as reported in patients and animal models of this disease. In the present study, we examined the status of cannabinoid CB(1) receptors in the basal ganglia of female and male Park-2 knockout mice, a genetic model of PD that progresses with no neuronal death and that may be considered representative of early and presymptomatic parkinsonian deficits. We found an increase in the density of CB(1) receptors in the substantia nigra compared to wild-type animals with no changes in other basal ganglia, although this occurred only in females. Despite this increase, the motor inhibition caused by the acute administration of the cannabinoid agonist Delta(9)-tetrahydrocannabinol to Park-2 knockout female mice was markedly of lesser magnitude compared with the response found in wild-type animals. By contrast, the administration of the CB(1) receptor antagonist SR141716 resulted in a hyperkinetic response in parkin-null mice, response that was almost absent in wild-type animals and that was accompanied by a decrease in tyrosine hydroxylase activity in the caudate-putamen. However, parkin-null male mice exhibited normal levels of CB(1) receptors in the substantia nigra and the remaining basal ganglia, with the only exception of a small decrease in the lateral part of the caudate-putamen. This was associated with an increase in mRNA levels for superoxide dismutase in this structure. In addition, the administration of Delta(9)-tetrahydrocannabinol to parkin-null male mice caused a motor inhibition that was significantly greater than in the case of their wild-type counterparts, and that was accompanied by an increase in tyrosine hydroxylase activity in the caudate-putamen. In summary, extending the data obtained in humans and animal models of basal ganglia neurodegeneration, changes in CB(1) receptors were also observed in parkin-null mice, a model of PD that may be considered representative of early stages of this disease. These changes are associated with differences in behavioral responses to cannabinoid agonists or antagonists between Park-2 knockout and wild-type mice, although parkin-null mice exhibited evident gender-dependent differences for both levels of CB(1) receptors and motor responses to agonists or antagonists.


The endogenous cannabinoid system works as a feedback signal controlling dopamine-induced facilitation of motor behaviors. The present study explored whether a single acute stimulation of CB1 cannabinoid receptors with (-)-Delta(9)-tetrahydrocannabinol (THC, 5 mg kg(-1) i.p.) results in modifications in the sensitivity to the acute behavioral effects of the dopamine D(2)/D(3) receptor agonist quinpirole (0.025, 0.25 and 1 mg kg(-1), s.c.) 24 h after THC administration. Cannabinoid pretreatment increased the sensitivity to quinpirole-induced hyperlocomotion 24 h after its administration. The data indicated that THC induced a
Desensitization of cannabinoid receptors, as revealed by a reduction in CB1 receptor-agonist induced GTP-gamma-S incorporation in striatal membranes. These results might be relevant for understanding the effect of cannabinoid exposure in dopamine-related neuropsychiatric disorders.


Implantation requires reciprocal interaction between blastocysts and a receptive uterus. In mice, one important player in this dialogue involves endocannabinoid signaling via cannabinoid receptor CB1. Anandamide is an endogenous cannabinoid ligand and its levels are spatiotemporally regulated in the uterus during early pregnancy, showing lower levels in the receptive uterus and at the implantation site. However, the mechanism by which differential uterine anandamide gradients are established under different pregnancy status is not clearly understood. Using multiple approaches, we show here that uterine anandamide levels conducive to implantation are primarily regulated by spatiotemporal expression of Nape-Pld, the gene encoding N-acylphosphatidyl-ethanolamine-hydrolyzing phospholipase D (NAPE-PLD) that generates anandamide. The expression is well correlated with its activity and anandamide levels. This study is clinically relevant, since elevated anandamide levels in peripheral circulation are associated with spontaneous pregnancy failure in women.


Binge alcohol consumption in the rat induces substantial neurodegeneration in the hippocampus and entorhinal cortex. Oxidative stress and cytotoxic edema have both been shown to be involved in such neurotoxicity, while NMDA receptor activity has been implicated in alcohol-withdrawal and excitotoxic injury. As the non-psychoactive cannabinoid, cannabidiol (CBD), was previously shown in vitro to prevent glutamate toxicity through its ability to reduce oxidative stress, we evaluated CBD as a neuroprotectant in a rat binge ethanol model. When administered concurrently with binge ethanol exposure, CBD protected against hippocampal and entorhinal cortical neurodegeneration in a dose-dependent fashion. Similarly, the common antioxidants butylated hydroxytoluene and alpha tocopherol also afforded significant protection. In contrast, the NMDA receptor antagonists MK-801 and memantine did not prevent cell death. Of the diuretics tested, furosemide was protective, whereas the other two anion exchanger inhibitors, L-644,711 and bumetanide were ineffective. In vitro comparison of these diuretics indicated that furosemide is also a potent antioxidant while the non-protective diuretics are not. The lack of efficacy of L-644,711 and bumetanide suggests that the antioxidant rather than the diuretic properties of furosemide contribute most critically to its efficacy in reversing ethanol-induced neurotoxicity in vitro, in our model. This study provides the first demonstration of CBD as an in vivo neuroprotectant and shows the efficacy of lipophilic antioxidants in preventing binge ethanol-induced brain injury.


Several molecular properties are calculated for a set of 26 cannabinoid compounds with the goal of connecting the psychoactivity of the compounds with an appropriate set of calculated properties. For this purpose we used quantum chemical (the AM1 semi-empirical method) and chemometric methods. The AM1 method was employed to calculate the set of quantum chemical molecular properties and the chemometric methods were employed with the aim of selecting the most relevant properties to be correlated with psychoactivity. The chemometric methods used were Principal Component Analysis (PCA), Hierarchical Cluster Analysis (HCA) and the K-Nearest Neighbor (KNN) method. The chemometric analysis showed that an electronic property (energy of LUMO), a hydrophobic property (log P), a steric property (volume of the substituent at the C4 position) and a topological property (Lovasz-Pelikan index) were the most important variables for the separation between the psychoactive and psychoinactive compounds. In order to validate our PCA, HCA and KNN results, eight new cannabinoid compounds (with known psychoactivity) were used in a prediction study and were classified correctly by the methods used.
in this work, indicating that our PCA, HCA and KNN models are able to predict reliable psychoactivity of cannabinoid compounds.


A novel solid-phase extraction (SPE) method was developed for extraction and cleanup of 11-nor-9-carboxy-delta9-tetrahydrocannabinol (THC-COOH), the major metabolite of the active principle of marijuana, delta9-tetrahydrocannabinol, from urine samples. The protocol utilizes a polymeric mixed-mode cationic sorbent, Strata-X-C, which exhibits strong retention for the metabolite facilitating a more rigorous organic wash to eliminate matrix components/endogenous materials. Acetonitrile containing acetic acid was used as the elution solvent and is compatible with both LC-MS and GC-MS modes of analysis. The hydrophobic retention of Strata-X-C was demonstrated to be higher than a neutral polymeric sorbent, Strata-X, of the same backbone but devoid of the cation-exchange moiety (sulfonic acid), by LC studies employing homologous paraben probes. Simultaneously, the polar (non-ionic) interaction capability of Strata-X-C is also greater than that of Strata-X, as assessed through regioisomeric nitrophenol probes. These two features enable the metabolite to be retained strongly on Strata-X-C. Good linearity and precision was obtained for THC-COOH by GC-MS analysis of its trimethylsilyl derivative in the range 1-50 ng. A simplified room temperature instantaneous derivatization procedure was developed that is suitable for high-throughput screening of THC-COOH.


Accelerated osteoclastic bone resorption has a central role in the pathogenesis of osteoporosis and other bone diseases. Identifying the molecular pathways that regulate osteoclast activity provides a key to understanding the causes of these diseases and to the development of new treatments. Here we show that mice with inactivation of cannabinoid type 1 (CB(1)) receptors have increased bone mass and are protected from ovariectomy-induced bone loss. Pharmacological antagonists of CB(1) and CB(2) receptors prevented ovariectomy-induced bone loss in vivo and caused osteoclast inhibition in vitro by promoting osteoclast apoptosis and inhibiting production of several osteoclast survival factors. These studies show that the CB(1) receptor has a role in the regulation of bone mass and ovariectomy-induced bone loss and that CB(1)- and CB(2)-selective cannabinoid receptor antagonists are a new class of osteoclast inhibitors that may be of value in the treatment of osteoporosis and other bone diseases.


Arachidonylethanolamide (anandamide, AEA) has been identified as an endogenous ligand for cannabinoid receptors CB1 and CB2. Characterization of the direct cannabimimetic actions of anandamide has been hampered by its short duration of action and rapid degradation in vivo and in vitro systems to arachidonic acid, a precursor in the biosynthesis of a broad range of biologically active molecules. In the present studies, we utilized 2-methylarachidonyl-(2'-fluoroethyl)amide (F-Me-AEA), an analog of anandamide resistant to enzymatic degradation, to determine whether F-Me-AEA modulated T cell function similar to that of plant-derived cannabinoids. Indeed, F-Me-AEA at low micromolar concentrations exhibited a marked inhibition of phorbol ester plus calcium ionophore (PMA/IO)-induced IL-2 protein secretion and steady state mRNA expression. Likewise, a modest suppression of the mixed lymphocyte response was observed in the presence of F-Me-AEA indicating an alteration in T cell responsiveness to allogeneic MHC class II antigens. F-Me-AEA was also found to modestly inhibit forskolin-stimulated adenylate cyclase activity in thymocytes and splenocytes, a hallmark of cannabinoid receptor agonists. Further characterization of the influence of F-Me-AEA on the cAMP signaling cascade revealed an inhibition of CREB-1/ATF-1 phosphorylation and subsequently, an inhibition of CRE DNA binding activity. Characterization of nuclear binding proteins further revealed that
NF-AT and, to a lesser extent, NF-kappaB DNA binding activities were also suppressed. These studies demonstrate that F-Me-AEA modulates T cell function in a similar manner to plant-derived and endogenous cannabinoids and therefore can be utilized as an amidase- and hydrolysis-resistant endogenous cannabinoid.


Endocannabinoids and ghrelin are potent appetite stimulators and are known to interact at a hypothalamic level. However, both also have important peripheral actions, including beneficial effects on the ischaemic heart and increasing adipose tissue deposition, while ghrelin has direct effects on carbohydrate metabolism. The AMP-activated protein kinase (AMPK) is a heterotrimeric enzyme which functions as a fuel sensor to regulate energy balance at both cellular and whole body levels, and it may mediate the action of anti-diabetic drugs such as metformin and PPAR agonists. Here we show that both cannabinoids and ghrelin stimulate AMPK activity in the hypothalamus and the heart, while inhibiting AMPK in liver and adipose tissue. These novel effects of cannabinoids on AMPK provide a mechanism for a number of their known actions, such as the reduction in infarct size in the myocardium, an increase in adipose tissue and stimulation of appetite. The beneficial effects of ghrelin on heart function, including reduction of myocyte apoptosis, and its effects on lipogenesis and carbohydrate metabolism, can also be explained by its ability to activate AMPK. Our data demonstrate that AMPK not only links the orexigenic effects of endocannabinoids and ghrelin in the hypothalamus, but also their effects on the metabolism of peripheral tissues.


Rodent models of neuropathic pain are used to investigate the underlying mechanisms of pain associated with damage to peripheral nerves and to evaluate the efficacy of novel compounds. However, few models have been adequately characterized and the validity of many models remains unclear. The present experiment examined the activity of known anti-allodynic compounds in the L5 spinal nerve ligation (SNL) model of peripheral mononeuropathy in the rat, a modified version of the L5/L6 SNL model [S.H. Kim, J.M. Chung, An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, Pain 50 (1992) 355-363]. Tactile sensitivity was measured 7-21 days post-surgery using von Frey monofilaments before and following treatment with gabapentin (30, 60 and 120mg/kg), morphine (1, 3 and 6mg/kg), amitriptyline (1.5, 3 and 10mg/kg), fluoxetine (3, 10 and 30mg/kg), WIN55,212-2 (0.5, 1 and 2.5mg/kg), indomethacin (1 and 5mg/kg) or U-50,488H (3 and 6mg/kg). Compared to sham-operated control animals, L5 SNL animals displayed significant tactile allodynia in the ipsilateral hindpaw that was completely reversed by treatment with gabapentin, morphine, and WIN55,212-2, partially reversed by amitriptyline and fluoxetine, and unaffected by U-50,488H or indomethacin. The robust effects of the non-selective cannabinoid receptor agonist WIN55,212-2 and morphine support reports in the literature that systemic cannabinoid receptor agonists and opioids are active in neuropathic pain. These results suggest that the L5 SNL model can be utilized to determine the anti-allodynic activity of novel compounds.


The proven clinical efficacy of the CB(1) cannabinoid receptor antagonist rimonabant in both obesity and smoking cessation and its therapeutic potential in other disorders has given a tremendous impetus to the discovery of novel CB(1) antagonists. The number of disclosed patents wherein novel chemical entities having CB(1) antagonistic or inverse agonistic properties have been claimed has exploded. Besides novel compound classes that were identified in screening, rational medicinal chemistry approaches such as conformational constraint and scaffold hopping have been successfully applied. CB(1) receptor modelling has provided insight into crucial receptor-ligand interaction points thereby leading to a general CB(1) inverse agonist pharmacophore model.

INTRODUCTION: The mammalian brain contains abundant G protein-coupled cannabinoid CB(1) receptors that respond to Delta(9)-tetrahydrocannabinol, the active ingredient of cannabis. The availability of a positron emission tomography (PET) radioligand would facilitate studies of the addictive and medicinal properties of compounds that bind to this receptor. Among the known classes of ligands for CB(1) receptors, the pyrazoles are attractive targets for radiopharmaceutical development because they are antagonists and are generally less lipophilic than the other classes. METHODS: A convenient high-yield synthesis of N-(4-[(18)F]fluorophenyl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1H-pyrazole-3-carboxamide (AM5144) was devised by coupling the appropriate pyrazole-3-carboxyl chloride compound with 4-[(18)F]fluoroaniline. The labeled precursor was synthesized from 1-[(18)F]fluoro-4-nitrobenzene in 60% radiochemical yield for 10 min using an improved procedure involving sodium borohydride reduction with cobalt chloride catalysis. The product was purified by HPLC to give a specific activity >400 mCi/mumol and a radiochemical purity >95%, and a PET study was conducted in a baboon. RESULTS: Although the regional uptake of AM5144 in baboon brain was consistent with binding to cannabinoid CB(1) receptors, absolute uptake at <0.003% injected radioactivity per cubic centimeter was lower than the previously reported uptake of the radioiodinated pyrazole AM281. CONCLUSIONS: The relatively poor brain uptake of AM5144 and other pyrazole CB(1) receptor ligands is not surprising because of their high lipophilicity as compared with most brain PET radiotracers. However, for nine pyrazole compounds for which rodent data are available, brain uptake and calculated logP values are not correlated. Thus, high logP values should not preclude evaluation of radiotracers for targets such as the CB(1) receptor that may require very lipophilic ligands.


An emerging body of evidence implicates peripheral and central endocannabinoid pathways in the regulation of feeding behavior and body weight. A report in this issue of the JCI demonstrates the presence of a common endocannabinoid-regulated molecular pathway for peripheral lipogenic and central appetitive regulation. This pathway involves the activation of the transcription factor SREBP-1c and its associated enzymes, acetyl-CoA carboxylase-1 and fatty acid synthase, in the liver and hypothalamus. Activation of cannabinoid receptor 1 (CB(1)) in liver plays a key role in increased serum lipid production, fatty liver, and possibly diet-induced obesity. Conversely, stimulation of these receptors in the hypothalamus may lead to an increase in food consumption. Thus, targeting both of these pathways with CB(1) antagonists could promote sustained weight loss and favorable serum lipid profiles in obese patients.


Substantial evidence suggests that all commonly abused drugs act upon the brain reward circuitry to ultimately increase extracellular concentrations of the neurotransmitter dopamine in the nucleus accumbens and other forebrain areas. Many drugs of abuse appear to increase dopamine levels by dramatically increase the firing and bursting rates of dopamine neurons located in the ventral mesencephalon. Recent clinical evidence in humans and behavioral evidence in animals indicate that cannabinoid receptor antagonists such as SR141716A (Rimonabant) can reduce the self-administration of, and craving for, several commonly addictive drugs. However, the mechanism of this potentially beneficial effect has not yet been identified. We propose, on the basis of recent studies in our laboratory and others, that these antagonists may act by blocking the effects of endogenously released cannabinoid molecules (endocannabinoids) that are released in an activity- and calcium-dependent manner from mesencephalic dopamine neurons. It is hypothesized that, through the antagonism of cannabinoid CB1 receptors located on inhibitory and excitatory axon terminals targeting the midbrain dopamine neurons, the effects of the endocannabinoids are occluded. The data from these studies therefore suggest that the endocannabinoid system and the CB1 receptors located...
in the ventral mesencephalon may play an important role in regulating drug reward processes, and that this substrate is recruited whenever dopamine neuron activity is increased.


AM 411 ((-)-1-adamantyl-Delta8-tetrahydrocannabinol) is a novel full agonist at cannabinoid CB1 receptors. The present studies were conducted to provide behavioral characterization of this compound in rats. It was hypothesized that AM 411 should produce behavioral effects similar to known cannabinoid agonists, and that these effects should be inhibited by co-treatment with a CB1 antagonist. In Experiments 1 and 2, AM 411 dose-dependently produced behaviors consistent with CB1 agonism, including analgesia, hypothermia, catalepsy and reductions in locomotion, which were blocked by a CB1-selective antagonist. In Experiment 3, AM 411 produced a dose-dependent suppression of lever-pressing on a fixed-ratio 5 (FR5) schedule, a task known to be sensitive to administration of CB1 agonists. Detailed analysis of the temporal patterns of operant responding showed that AM 411 altered the distribution of interresponse times. Experiment 4 showed that AM 411 decreased relative interior activity in the open field, which is suggestive of an anxiogenic effect. It is concluded that AM 411 produces CB1 agonist-like behavior with potency between that of WIN 55,212-2 and AM 356. AM 411 could be a useful tool for understanding the behavioral and neural effects of CB1 receptor stimulation.

Naderi, N., B. Shafaghi, et al. (2005). "Interaction between gamma-aminobutyric acid GABA(B) and cannabinoid CB(1) receptors in spinal pain pathways in rat." Eur J Pharmacol 514(2-3): 159-64.

Antinociceptive effects of cannabinoids are mediated, in part, at the spinal level. Cannabinoid CB(1) receptors are co-localized with dorsal horn interneurons containing gamma-aminobutyric acid (GABA). In this study, we investigated the interaction between intrathecally administered cannabinoid and GABA(B) receptor agonists and antagonists in the modulation of formalin-induced pain at the spinal level. Intrathecal pretreatment of rats with a cannabinoid receptor antagonist [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-[2,4-dichlorophenyl]-4-methyl-1-H -pyrazole-3-carboxamide] (SR141716A, 30 mug) decreased the analgesic effect of the intrathecal administration of the GABA(B) receptor agonist, baclofen (0.125 mug and 0.25 mug). Intrathecal administration of the GABA(B) receptor antagonist, saclofen (30 mug), 10 min before administration of the cannabinoid receptor agonist (-)-cis-3-[2-hydroxy-4-((1,1-dimethylheptyl)-phenyl)-trans-4-(3-hydroxy-pro pyl)-cyclohexano (CP55940), did not affect the analgesia produced by the cannabinoid receptor agonist. Our results confirm that intrathecal administration of cannabinoid and GABA(B) receptor agonists have analgesic effects and that spinal antinociceptive effects of GABA(B) receptor agonists are likely through endocannabinoid modulation.


Endogenous cannabinoids acting at CB(1) receptors stimulate appetite, and CB(1) antagonists show promise in the treatment of obesity. CB(1) (-/-) mice are resistant to diet-induced obesity even though their caloric intake is similar to that of wild-type mice, suggesting that endocannabinoids also regulate fat metabolism. Here, we investigated the possible role of endocannabinoids in the regulation of hepatic lipogenesis. Activation of CB(1) in mice increases the hepatic gene expression of the lipogenic transcription factor SREBP-1c and its targets acetyl-CoA carboxylase-1 and fatty acid synthase (FAS). Treatment with a CB(1) agonist also increases de novo fatty acid synthesis in the liver or in isolated hepatocytes, which express CB(1). High-fat diet increases hepatic levels of the endocannabinoid anandamide (arachidonoyl ethanolamide), CB(1) density, and basal rates of fatty acid synthesis, and the latter is reduced by CB(1) blockade. In the hypothalamus, where FAS inhibitors elicit anorexia, SREBP-1c and FAS expression are similarly affected by CB(1) ligands. We conclude that anandamide acting at
hepatic CB(1) contributes to diet-induced obesity and that the FAS pathway may be a common molecular target for central appetitive and peripheral metabolic regulation.


Cannabinoids and their endogenous and synthetic analogs exert powerful hypotensive and cardiodepressor effects by complex mechanisms involving direct and indirect effects on myocardium and vasculature. On the one hand, endocannabinoids and cannabinoid receptors have been implicated in the hypotensive state associated with hemorrhagic, endotoxic and cardiogenic shock, and advanced liver cirrhosis. On the other hand, there is emerging evidence suggesting that the endocannabinergic system plays an important role in the cardiovascular regulation in hypertension. This review is aimed to discuss the in vivo hypotensive and cardiodepressant effects of cannabinoids mediated by cannabinoid and TRPV(1) receptors, and focuses on the novel therapeutical strategies offered by targeting the endocannabinoid system in the treatment of hypertension.


Previous experiments showed that R-(+)-WIN55212-induced inhibition of electrically-evoked contractions of mouse vasa deferentia could be antagonized by cannabidiol in a manner that appeared to be competitive but not to involve direct competition for established cannabinoid receptors. We have now discovered that (-)-7-hydroxy-4'-dimethylheptyl-cannabidiol (7-OH-DMH-CBD) inhibits electrically-evoked contractions of the vas deferens (EC(50)=13.3nM). This it appeared to do by acting on prejunctional neurones as 100nM 7-OH-DMH-CBD did not attenuate contractile responses to phenylephrine or beta, gamma-methylene-ATP. Although 7-OH-DMH-CBD was antagonized by SR141716A, it was less susceptible to antagonism by this CB(1) receptor antagonist than R-(+)-WIN55212. 7-OH-DMH-CBD was also antagonized by cannabidiol (1muM; apparent K(B)=222.2nM) but not by the CB(2) receptor antagonist, SR144528 (32nM), or by naloxone (300nM), ruthenium red (1muM) or capsazepine (10muM). Yohimbine (100nM) enhanced the ability of 7-OH-DMH-CBD to inhibit electrically-evoked contractions. R-(+)-WIN55212 was also potentiated by 100nM yohimbine, possibly reflecting ongoing sequestration of G(i/o) proteins from CB(1) receptors by alpha(2)-adrenoceptors. Our results suggest that 7-OH-DMH-CBD may activate a neuronal target in the vas deferens that is not a CB(1), CB(2), TRPV1, opioid or alpha(2)-adrenergic receptor but do not exclude the possibility that it also activates CB(1) receptors.


Since the discovery of the cannabinoid CB2 receptor in 1993, there has been a growing interest to clarify the importance of this G-protein coupled receptor (GPCR) for human physiology, and to investigate it as a possible target for current and future drug development. Several mutation studies have examined the receptor activation and structure of the receptor binding cavity. Additionally, 3D models for the CB2 receptor have been constructed to aid in perceiving important ligand-receptor interactions. In recent years, many research groups have succeeded in synthesizing new CB2 selective ligands. This review focuses on (i) important features for ligand recognition and/or receptor activation at CB2, derived from mutation and modeling studies, and (ii) recent advances in the field of CB2 selective ligands.


Cerebellar Purkinje cells (PCs) receive GABAergic input that undergoes powerful retrograde modulation by presynaptic cannabinoid and glutamate receptors. Here we examine a distinct modulatory mechanism at these synapses, which does not require postsynaptic depolarization and acts via presynaptic AMPA receptors. We find that this mechanism operates mainly in the somatic vicinity of PCs in which large boutons of basket cell axons form synapses...
on the PC soma. We use fast confocal microscopy and detailed kinetic modeling to estimate that, in these boutons, an action potential opens 100-200 Ca2+ channels, eliciting a brief 3-5 microM transient, followed by a longer-term, 15-30 nM rise of free Ca2+ (above the resting level of approximately 100 nM). Brief activation of local AMPA receptors suppresses Ca2+ entry (probably by silencing 20-40 P/Q-type channels) in a subgroup of terminals that tend to show a higher dynamic range of Ca2+ signaling. The results provide the first quantitative description of presynaptic Ca2+ kinetics and its modulation by AMPA receptor activation (most likely via a glutamate spillover-mediated mechanism) at identified GABAergic synapses.


Previously, we have shown that microinjection of endocannabinoids (ECBs) into the nucleus tractus solitarius (NTS) can modulate baroreflex control of blood pressure (BP), prolonging pressor-induced inhibition of renal sympathetic nerve activity. This suggests that ECBs can modulate excitability of baroreceptive neurons in the NTS. Studies by others have shown that neural cannabinoid (CB(1)) receptors are present on fibers in the NTS, suggesting that some presynaptic modulation of transmitter release could occur in this region which receives direct afferent projections from arterial baroreceptors and cardiac mechanoreceptors. This study, therefore, was performed to determine the effects of ECBs on NTS baroreceptive neuronal discharge. Picoinjection of the ECB anandamide (AEA) was found to significantly increase discharge of baroreceptive neurons (20 of 23). Picoinjection of the ECB uptake inhibitor, AM404, which enhances endogenous ECB activity, also significantly increased discharge of baroreceptive neurons (8 of 10 neurons). To determine if effects of ECBs involved a GABAA mechanism, the neuronal responses to AEA and AM404 were tested after prior blockade of postsynaptic GABAA receptors by bicuculline (BIC) or SR 95531 hydrobromide (gabazine-SR 95531), which would eliminate any effects due to modulation of GABA input. The increase in neuronal discharge to both AEA and AM404 was significantly attenuated following BIC or SR 95531, which alone significantly increased discharge of baroreceptive neurons tested. These results support the hypothesis that ECBs enhance baroreflex function through increases in NTS baroreceptive neuronal activity, due in part to modulation of GABAergic inhibitory effects at the neuronal level.


Noladin ether (NE) is a putative endogenously occurring cannabinoid demonstrating agonist activity at CB1 receptors. Because of reported selective affinity for CB1 receptors, the pharmacological actions of NE at CB2 receptors have not been examined. Therefore, the purpose of this study was to characterize the binding and functional properties of NE at human CB2 receptors stably expressed in CHO cells, as well as in HL-60 cells which express CB2 receptors endogenously. Surprisingly, in transfected CHO cells, NE exhibits a relatively high nanomolar affinity for CB2 receptors (Ki = 480 nM), comparable to that observed for the endocannabinoid 2-arachidonoyl glycerol (2-AG) (Ki = 1016 nM). Furthermore, NE activates G-proteins and inhibits the intracellular effector adenylyl cyclase with equivalent efficacy relative to the full cannabinoid agonists 2-AG and CP 55,940 (CP). The rank order of potency for G-protein activation and effector regulation by the three agonists is similar to their apparent affinity for CB2 receptors; CP > NE ? 2-AG. Regulation of adenylyl cyclase activity by all agonists is inhibited by pertussis toxin pre-treatment or by co-incubation with AM630, a CB2 antagonist. Chronic treatment with NE or CP results in CB2 receptor desensitization and down-regulation. All agonists also inhibit adenylyl cyclase activity in HL-60 cells. Taken collectively, these data indicate that NE acts as a full agonist at human CB2 receptors and thus might have important physiological functions at peripheral cannabinoid receptors.

Solinas, M., L. V. Panlilio, et al. (2005). "Cannabinoid Agonists but not Inhibitors of Endogenous Cannabinoid Transport or Metabolism Enhance the Reinforcing Efficacy of Heroin in Rats." *Neuropsychopharmacology*.

Accumulating evidence suggests that the endogenous cannabinoid system is involved in the reinforcing effects of heroin. In rats intravenously self-administering heroin, we investigated
effects of cannabinoid CB(1) receptor agonists and compounds that block transport or metabolism of the endogenous cannabinoid anandamide. The natural cannabinoid CB(1) receptor agonist delta-9-tetrahydrocannabinol (THC, 0.3-3 mg/kg i.p.) did not alter self-administration of heroin under a fixed-ratio one (FR1) schedule, except at a high 3 mg/kg dose which decreased heroin self-administration. Under a progressive-ratio schedule, however, THC dose-dependently increased the number of 50 μg/kg heroin injections self-administered per session and the maximal ratio completed (break-point), with peak increases at 1 mg/kg THC. In addition, 1 mg/kg THC increased break-points and injections self-administered over a wide range of heroin injection doses (25-100 μg/kg), indicating an increase in heroin's reinforcing efficacy and not its potency. The synthetic cannabinoid CB(1) receptor agonist WIN55,212-2 (0.3-3 mg/kg i.p.) had effects similar to THC under the progressive-ratio schedule. In contrast, AM-404 (1-10 mg/kg i.p.), an inhibitor of transport of anandamide, and URB-597 (0.01-0.3 mg/kg i.p.), an inhibitor of the enzyme fatty acid amide hydrolase (FAAH) that degrades anandamide, or their combination, did not increase reinforcing efficacy of heroin at any dose tested. Thus, activation of cannabinoid CB(1) receptors facilitates the reinforcing efficacy of heroin and this appears to be mediated by interactions between cannabinoid CB(1) receptors and μ-opioid receptors and their signaling pathways, rather than by an opioid-induced release of endogenous cannabinoids.


In this study, we have determined the contractile effects of CB1 and CB2 cannabinoid receptor activation on rat isolated atria and the different signaling pathways involved. Anandamide did not have a significantly effect on atria contractility, however, the treatment with both CB1 (AM251) or CB2 (AM630) receptor antagonists, the endocannabinoids triggered stimulation or inhibition on contractility respectively. The ACEA stimulation of CB1 receptor exerted decrease on contractility, that significantly correlated with the decrement of cAMP and the stimulation of nitric oxide synthase (NOS) and the accumulation of cyclic GMP (cGMP). On the contrary, JWH 015 stimulation of CB2 receptor triggered positive contractile response that significantly correlated with the increase cAMP production. The inhibition of adenylate cyclase activity impaired the JWH 015 activation of CB1 receptor induced positive contractile effect, while inhibitors of phospholipase C (PLC), NOS and soluble nitric oxide (NO)-sensitive guanylate cyclase blocked the dose-response curves of ACEA on contractility. Those inhibitors also attenuated the CB1 receptor-dependent increase in activation of NOS and cGMP accumulation. These results suggest that CB2 receptor agonist mediated positive contractile effect associated with increased production on cAMP while CB1 receptor agonist mediated decrease on contractility associated with decreased cAMP accumulation and increase production of NO and cGMP; that occur secondarily to stimulation of PLC, NOS and soluble guanylate cyclase. Data give pharmacological evidence for the existence of functional CB1 and CB2 cannabinoid receptors in rat isolated atria and may contribute to a better understanding the effects of cannabinoids in the cardiovascular system.


Prostanoids and cannabinoids have ocular hypotensive and neuroprotective properties. The effect of the prostanoid AH13205 (EP2), the thromboxane-mimetic U46619, the cannabinoid (CB) agonists WIN55212-2 and CP 55,940, endothelin-1 (ET-1) and 8-bromo-cAMP on the membrane currents of trabecular meshwork (TM) cells were measured using the patch-clamp technique and compared to their effects on TM contractility. Previous studies show relaxation of TM to AH 13205 and other substances that elevate cAMP, while U46619 and endothelin-1 contract TM. This study shows that after contraction (100%) with carbachol (10(-6)m), the CB agonist CP 55,940 dose-dependently reduced contractility to 83+/-4% (n=9) (10(-6)m) and 61+/-10%, (n=7) (10(-5)m). In the presence of both the CB1 antagonist AM251 (10(-6)m) and CP
55,940 (10(-5)m), the contractile response to carbachol reached 84+/−3% (n=6) of the original level. In patch-clamp experiments, membrane permeable 8-bromo-cAMP (10(-4)m) had no effect on currents of TM cells. In contrast, AH 13205 and two cannabinoids reversibly enhanced outward current through high-conductance Ca(2+)-activated K(+) channels (BKCa, BK, maxi-K) to the following values (in % of the initial value at 100mV): AH 13205 (10(-5)m): 200+/−28% (n=6), CP 55,940 (10(-6)m): 196+/−33% (n=7), CP 55,940 (10(-5)m): 484+/−113% (n=7), WIN55212-2 (10(-5)m): 205+/−41% (n=10). Iberiotoxin (10(-7)m) completely blocked these responses. The current response to CP 55,940 (10(-5)m) could be partially blocked by the CB1 antagonist AM251 (10(-6)m). Conversely, the contractile agents in this study either caused a transient reduction in outward current (ET-1(5x10(-8)m)) or had no effect (U46619 (10(-6)m)). We conclude that stimulation of EP2 and CB1 receptors in TM is coupled to the activation of BKCa channels via a non-diffusible second messenger cascade. This effect may contribute to the relaxant activity of EP2 and CB1 agonists in isolated TM strips, modulating ocular outflow.


Delta(9)-THC and synthetic cannabinoids produce memory impairment in humans as well as in laboratory animals. The high concentration of cannabinoid CB1 receptors and the presence of endocannabinoids in the hippocampus suggest that a cannabinoid neurochemical system may play a role in learning and memory processes. Thus, the objective of the present work was to study the effect of the cannabinoid antagonist SR141716A (SR) on memory acquisition, consolidation and retrieval in a recently developed elevated T-maze (ETM) model of anxiety and memory. In addition, we investigated whether pre-training SR administration was capable of reversing scopolamine-induced memory impairment. Adult male mice were exposed to the closed arm as many times as necessary for the animals to reach the avoidance criterion of remaining in the closed arm for 300s; they were then tested (exposed to the closed arm) 24h and 7 days after the training. SR (0.5, 1.0 or 2.0mg/kg) was administered i.p. 20min before the training, immediately after training or 20min before the test in the mice. The elevated plus-maze (EPM) was used to investigate a possible influence of SR on locomotion and on the anxiety-related behavior. SR provoked memory improvement, which was observed when the drug was administered before (effect on memory acquisition/consolidation) or immediately after the training (effect on memory consolidation), but not when the drug was administered before the test (effect on memory retrieval). Also, SR administration reversed scopolamine-induced amnesia. These effects were observed in the absence of changes in locomotion or anxiety levels. Our results demonstrate that the blockade of cannabinoid receptors may improve memory acquisition and consolidation in the ETM model.


Cannabinoids regulate biological processes governed by the hypothalamus including, but not limited to, energy homeostasis and reproduction. The present study sought to determine whether cannabinoids modulate a-type K(+) currents (IA) in neurons of the hypothalamic arcuate nucleus (ARC). Whole-cell patch clamp recordings were performed in slices through the ARC prepared from castrated female and male guinea pigs. Forty percent of guinea pig ARC neurons exhibited a transient outward current that was antagonized by high (mM) concentrations of 4-aminopyridine and (100 nM) rHeteropodatoxin-2. Five of these neurons also were immunopositive for both beta-endorphin and the Kv4.2 channel subunit. Bath application of the CB1 receptor agonists WIN 55,212-2 (1 microM) or ACEA (1 microM) selectively induced a rightward shift in the inactivation curve for the IA, significantly increasing the half-maximal voltage without affecting the peak current magnitude, in neurons from female but not male animals. The CB1 receptor antagonist AM251 (1 microM) reversed this action. Collectively, these data reveal that guinea pig ARC neurons, including proopiomelanocortin neurons, express a prominent IA that is positively modulated by cannabinoids in a sex-specific way by altering the voltage dependence of its inactivation. The resultant inhibitory effect on this neuronal population may shed some insight into the mechanism(s) by which cannabinoids influence hypothalamic function.

Endocannabinoids and cannabinoid CB1 receptors play a role in the control of movement by modulating GABA, glutamate, and other neurotransmitters throughout the basal ganglia. Roles for abnormalities in endocannabinoid signaling in Parkinson's disease (PD) and the major side effect of current treatments, levodopa-induced dyskinesia (LID), have been suggested by rodent studies. Here we show that signaling by endocannabinoids contributes to the pathophysiology of parkinsonism and LID in MPTP-lesioned, non-human primate models of Parkinson's disease. In MPTP-lesioned marmosets previously treated with levodopa to establish LID, attenuation of CB1 signaling by systemic administration of rimonabant (1 and 3 mg/kg) had anti-parkinsonian actions, equivalent to a 71% increase in motor activity at 3 mg/kg. Rimonabant did not elicit dyskinesia. Co-administration of levodopa (8 mg/kg) and rimonabant (1 and 3 mg/kg) resulted in significantly less dyskinesia than levodopa alone, without significantly affecting the anti-parkinsonian action of levodopa. These data suggest that enhanced endocannabinoid signaling may be involved in the pathophysiology of both parkinsonism and LID. To define potential mechanisms by which such a role might be mediated, we determined the levels of the endocannabinoids anandamide and 2-arachidonyl glycerol (2-AG) throughout the basal ganglia in normal and three groups of MPTP-lesioned cynomolgus monkeys (untreated; acutely treated with L-DOPA, non-dyskinetic; long-term treated, with levodopa-induced dyskinesia). In the untreated, MPTP-lesioned primate, parkinsonism was associated with increases in both 2-AG (+88%) and anandamide (+49%) in the striatum, and of 2-AG (+97%) in the substantia nigra, changes that are consistent with the previously suggested role for endocannabinoids in mechanisms attempting to compensate for loss of dopamine in untreated parkinsonism. Increased levels of anandamide (+34%) in the external globus pallidus of MPTP-lesioned animals were normalized by levodopa treatment and may contribute to the generation of parkinsonian symptoms. However, no clear alteration in endocannabinoid levels could be correlated with the expression of LID. These data highlight the potential roles played by endocannabinoids and CB1 in PD and LID and suggest the need for further research to pursue the multiple therapeutic opportunities for manipulating this system in movement disorders.


In the globus pallidus, cannabinoid CB1(1) receptors are localized pre-synaptically on GABAergic neurons. We assessed the influence of the endocannabinoids, anandamide, 2-arachidonoyl-glycerol (2-AG) and noladin ether, on the uptake of [(3)H]-GABA in pallidal slices from rat. Both 2-AG and noladin ether increased [(3)H]-GABA uptake (by 40.8 +/- 8.0% and 38.4 +/- 12.5%). The effect of 2-AG was blocked by the cannabinoid CB(1) receptor antagonist AM 251. In contrast, neither anandamide nor the agonist WIN 55,212-2 had an effect on [(3)H]-GABA uptake. Different roles might be played by different endocannabinoids, both physiologically and in basal ganglia disorders, such as Parkinson's disease.


We examined the effects of a cannabinoid receptor agonist, (R)-(+-)[2,3-dihydro-5-methyl-3-[(4-merpholino)methyl]pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl][1-naphthyl]methanone (WIN 55212-2), on various respiratory reactions induced by the activation of capsaicin-sensitive afferent sensory nerves (C-fibers). WIN 55212-2 significantly inhibited capsaicin-induced guinea pig bronchoconstriction, but not the neurokinin A-induced reaction. Intravenous injection of WIN 55212-2 also blocked cigarette smoke-induced rat tracheal plasma extravasation. However, substance P-induced rat tracheal plasma extravasation was not affected by the administration of WIN 55212-2. A cannabinoid CB(2) receptor antagonist, {N-[(S)-endo-1,3,3-trimethylbicyclo[2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzy1)pyrazole-3-carboxamide} (SR 144528) reduced the inhibitory effects of WIN 55212-2, but not a cannabinoid CB(1) antagonist, [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-
pyrazole-3-carboxamidehydrochloride] (SR 141716A). A Maxi-K(+) channel opener, 1-(2' -hydroxy-5'-trifluoromethylphenyl)-5-trifluoromethyl-2(3H)benzimidazole lone (NS 1619), specifically inhibited capsaein-induced guinea pig bronchoconstriction and cigarette smoke-induced rat tracheal plasma extravasation. These findings suggest that WIN 55212-2 inhibits the activation of C-fibers via cannabinoid CB(2) receptors and Maxi-K(+) channels and reduces airway neurogenic inflammatory reactions in vivo.


2-arachidonoylglycerol (2-AG) is the most abundant endocannabinoid and it plays a critical role in cannabinoid receptor-mediated cell signaling. Although 2-AG was shown to induce ERK activation via the cannabinoid receptor 1 (CB1), only a nonspecific CB receptor agonist and antagonist was used in those studies. Whether cannabinoid receptor 2 (CB2) is involved in 2-AG-induced ERK activation is still unclear. Moreover, whether 2-AG is involved in mediation of AP-1 activity and cell transformation is also not known. In the present study, we show that 2-AG stimulates AP-1-dependent transcriptional activity and enhances EGF-induced cell transformation in mouse epidermal JB6 P+ Cl41 cells. Using JB6 P+ C141 cells, stably transfected with an AP-1 luciferase reporter, we found that 10 microM 2-AG induced up to a 3-fold stimulation of AP-1 transcriptional activity. The AP-1 stimulation appeared to be mediated by ERK, but not JNK or p38 kinase. PD98059, a specific inhibitor of MEK1, almost completely blocked 2-AG-induced ERKs phosphorylation and AP-1 activation. Using CB1/2-/- murine embryonic fibroblasts (MEFs), we present the first direct evidence that both of cannabinoid receptors 1 and 2 (CB1/2) are involved in 2-AG-induced ERK activation. 2-AG could not stimulate ERK phosphorylation or Fyn kinase activity in dominant negative Fyn. In addition, the Fyn inhibitor, PP2, blocked 2-AG-induced Fyn kinase activity and ERKs phosphorylation and activity. siRNA Fyn also suppressed 2-AG-induced ERKs phosphorylation. Interestingly, 2-AG enhanced EGF-induced AP-1 DNA binding and cell transformation. Taken together, our data provide direct evidence suggesting that 2-AG may have a novel role in cell transformation and carcinogenesis in a signaling pathway involving CB1/2 and activation of Fyn, ERKs and AP-1.


Exogenously administered cannabinoids are neuroprotective in several different cellular and animal models. In the current study, two cannabinoid CB1 receptor ligands (WIN 55,212-2, CP 55,940) markedly reduced hippocampal cell death, in a time-dependent manner, in cultured neurons subjected to high levels of NMDA (15muM). WIN 55,212-2 was also shown to inhibit the NMDA-induced increase in intracellular calcium concentration ([Ca(2+)][i]) indicated by FURA-2 fluorescence imaging in the same cultured neurons. Changes in [Ca(2+)][i] occurred with similar concentrations (25-100nM) and in the same time-dependent manner (pre-exposure 1-15min) as CB1 receptor mediated neuroprotective actions. Both effects were blocked by the CB1 receptor antagonist SR141716A. An underlying mechanism was indicated by the fact that (1) the NMDA-induced increase in [Ca(2+)][i] was inhibited by ryanodine, implicating a ryanodine receptor (RyR) coupled intracellular calcium channel, and (2) the cannabinoid influence involved a reduction in cAMP cAMP-dependent protein kinase (PKA) dependent phosphorylation of the same RyR levels that regulate channel. Moreover the time course of CB1 receptor mediated inhibition of PKA phosphorylation was directly related to effective pre-exposure intervals for cannabinoid neuroprotection. Control studies ruled out the involvement of inositol-trisphosphate (IP3) pathways, enhanced calcium reuptake and voltage sensitive calcium channels in the neuroprotective process. The results suggest that cannabinoids prevent cell death by initiating a time and dose dependent inhibition of adenyl cyclase, that outlasts direct action at the CB1 receptor and is capable of reducing [Ca(2+)][i] via a cAMP/PKA-dependent process during the neurotoxic event.
CLINICAL SCIENCE


Bipolar affective disorder is often poorly controlled by prescribed drugs. Cannabis use is common in patients with this disorder and anecdotal reports suggest that some patients take it to alleviate symptoms of both mania and depression. We undertook a literature review of cannabis use by patients with bipolar disorder and of the neuropharmacological properties of cannabinoids suggesting possible therapeutic effects in this condition. No systematic studies of cannabinoids in bipolar disorder were found to exist, although some patients claim that cannabis relieves symptoms of mania and/or depression. The cannabinoids Delta(9)-tetrahydrocannabinol (THC) and cannabidiol (CBD) may exert sedative, hypnotic, anxiolytic, antidepressant, antipsychotic and anticonvulsant effects. Pure synthetic cannabinoids, such as dronabinol and nabilone and specific plant extracts containing THC, CBD, or a mixture of the two in known concentrations, are available and can be delivered sublingually. Controlled trials of these cannabinoids as adjunctive medication in bipolar disorder are now indicated.


Persistent dose-related cognitive decrements have been reported in 28-day abstinent heavy marijuana (MJ) users. However, the neural substrates of these decrements in cognitive performance are not known. This study aimed to determine if 25-day abstinent MJ users show persistent dose-related alterations in performance and brain activity using PET H(2)(15)O during the Iowa Gambling Task-IGT (a decision-making task). Eleven heavy MJ users and 11 non-drug users participated. The MJ group resided in an inpatient research unit at the NIH/NIDA-IRP for 25 days prior to testing to ensure abstinence. A dose-related association was found between increased MJ use and lower IGT performance and alterations in brain activity. The MJ group showed greater activation in the left cerebellum and less activation in the right lateral orbitofrontal cortex (OFC) and the right dorsolateral prefrontal cortex (DLPFC) than the Control group. When the MJ group was divided into Moderate (8-35 joints/week) and Heavy users (53-84 joints/week), the Heavy MJ group showed less activation in the left medial OFC and greater activation in the left cerebellum than the Moderate group. However, brain activity and task performance were similar between the Moderate MJ users and the Control group, suggesting a "threshold effect". These preliminary findings indicate that very heavy users of MJ have persistent decision-making deficits and alterations in brain activity. Specifically, the Heavy MJ users may focus on only the immediate reinforcing aspects of a situation (i.e., getting high) while ignoring the negative consequences. Thus, faulty decision-making could make an individual more prone to addictive behavior and more resistant to treatment. Finally, it is unclear if these neurologic findings will become progressively worse with continued heavy MJ use or if they will resolve with abstinence from MJ use.


BACKGROUND: Recent evidence documents that cannabis use by young people is a modest statistical risk factor for psychotic symptoms in adulthood, such as hallucinations and delusions, as well as clinically significant schizophrenia. The vast majority of cannabis users do not develop psychosis, however, prompting us to hypothesize that some people are genetically vulnerable to the deleterious effects of cannabis. METHODS: In a longitudinal study of a representative birth cohort followed to adulthood, we tested why cannabis use is associated with the emergence of psychosis in a minority of users, but not in others. RESULTS: A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis. Carriers of the COMT valine(158) allele
were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis use had no such adverse influence on individuals with two copies of the methionine allele. CONCLUSIONS: These findings provide evidence of a gene x environment interaction and suggest that a role of some susceptibility genes is to influence vulnerability to environmental pathogens.


OBJECTIVE: To examine the recent evidence that marijuana and other cannabinoids have therapeutic potential. METHODS: Literature published since 1997 was searched using the following terms: cannabinoid, marijuana, THC, analgesia, cachexia, glaucoma, movement, multiple sclerosis, neurological, pain, Parkinson, trial, vomiting. Qualifying clinical studies were randomized, double-blind, and placebo-controlled. Selected open-label studies and surveys are also discussed. RESULTS: A total of 15 independent, qualifying clinical trials were identified, of which only three had more than 100 patients each. Two large trials found that cannabinoids were significantly better than placebo in managing spasticity in multiple sclerosis. Patients self-reported greater sense of motor improvement in multiple sclerosis than could be confirmed objectively. In smaller qualifying trials, cannabinoids produced significant objective improvement of tics in Tourette's disease, and neuropathic pain. A new, non-psychotropic cannabinoid also has analgesic activity in neuropathic pain. No significant improvement was found in levodopa-induced dyskinesia in Parkinson's Disease or post-operative pain. No difference from active placebo was found for management of cachexia in a large trial. Some immune system parameters changed in HIV-1 and multiple sclerosis patients treated with cannabinoids, but the clinical significance is unknown. Quality of life assessments were made in only three of 15 qualifying clinical trials. CONCLUSION: Cannabinoids may be useful for conditions that currently lack effective treatment, such as spasticity, tics and neuropathic pain. New delivery systems for cannabinoids and cannabis-based medicinal extracts, as well as new cannabinoid derivatives expand the options for cannabinoid therapy. More well-controlled, large clinical tests are needed, especially with active placebo.


Cannabis is the most widely used illicit drug. Despite this, only a small number of studies have investigated the long-term neurotoxic consequences of cannabis use. Structural and functional neuroimaging techniques are powerful research tools to investigate possible cannabis-induced pathophysiological changes. A computer literature review was conducted in the MEDLINE and PsycLIT databases between 1966 and November of 2004 with the search terms 'cannabis', 'marijuana', 'neuroimaging', 'magnetic resonance', 'computed tomography', 'positron emission tomography', 'single photon emission computed tomography', 'SPET', 'MRI' and 'CT'. Structural neuroimaging studies have yielded conflicting results. Most studies report no evidence of cerebral atrophy or regional changes in tissue volumes, and one study suggested that long-term users who started regular use on early adolescence have cerebral atrophy as well as reduction in gray matter. However, several methodological shortcomings limit the interpretation of these results. Functional neuroimaging studies have reported increases in neural activity in regions that may be related with cannabis intoxication or mood-change effects (orbital and mesial frontal lobes, insula, and anterior cingulate) and decreases in activity of regions related with cognitive functions impaired during acute intoxication. The important question whether residual neurotoxic effects occur after prolonged and regular use of cannabis remains unclear, with no study addressing this question directly. Better designed neuroimaging studies, combined with cognitive evaluation, may be elucidative on this issue.


The endogenous cannabimimetic compound, and anandamide analogue, N-palmitoyl-ethanolamine (PEA), was shown to exert potent anti-inflammatory and analgesic effects in
experimental models of visceral, neuropathic and inflammatory pain by acting via several possible mechanisms. However, only scant data have been reported on the regulation of PEA levels during pathological conditions in animals or, particularly, humans. We review the current literature on PEA and report the results of three separate studies indicating that its concentrations are significantly increased during three different inflammatory and neuropathic conditions, two of which have been assessed in humans, and one in a mouse model. In patients affected with chronic low back pain, blood PEA levels were not significantly different from those of healthy volunteers, but were significantly and differentially increased (1.6-fold, P<0.01, N=10 per group) 30 min following an osteopathic manipulative treatment. In the second study, the paw skin levels of PEA in mice with streptozotocin-induced diabetic neuropathic pain were found to be significantly higher (1.5-fold, P<0.005, N=5) than those of control mice. In the third study, colonic PEA levels in biopsies from patients with ulcerative colitis were found to be 1.8-fold higher (P<0.05, N=8-10) than those in healthy subjects. These heterogeneous data, together with previous findings reviewed here, substantiate the hypothesis that PEA is an endogenous mediator whose levels are increased following neuroinflammatory or neuropathic conditions in both animals and humans, possibly to exert a local anti-inflammatory and analgesic action.


Studies of the consequences of prenatal marijuana use have reported effects predominantly on the behavioral and cognitive development of the children. Research on other aspects of child neurobehavioral development, such as psychiatric symptomatology, has been limited. This study examines the relations between prenatal marijuana exposure (PME) and child depressive symptoms at 10 years of age. Data are from the 10-year follow-up of 633 mother-child dyads who participated in the Maternal Health Practices and Child Development Project. Maternal prenatal and current substance use, measures of the home environment, demographic status, and psychosocial characteristics were ascertained at prenatal months four and seven, at delivery, and at age 10. At age 10, the children also completed the Children's Depression Inventory (CDI) [M. Kovacs. The Children's Depression Inventory, Multi-Health Systems, Inc., North Tonawanda, NY, (1992).], a self-report measure of current depressive symptoms. Multivariate regressions were used to test trimester-specific effects of marijuana and their associations with the CDI total score, while controlling for significant prenatal predictors and significant current covariates of childhood depression. PME in the first and third trimesters predicted significantly increased levels of depressive symptoms. This finding remained significant after controlling for all identified covariates from both the prenatal period and the current phase at age 10. These findings reflect an association with the level of depressive symptoms rather than a diagnosis of a major depressive disorder. Other significant correlates of depressive symptoms in the children included maternal education, maternal tobacco use (prenatal or current), and the child's composite IQ score. These findings are consistent with recent reports that identify specific areas of the brain and specific brain functions that are associated with PME.


Cannabinoids present in Cannabis sativa (marijuana) exert biological effects via cannabinoid receptors CB1 and CB2. We recently demonstrated that CB1 and CB2 receptors regulate progression of experimental liver fibrosis. We therefore investigated the impact of cannabis smoking on fibrosis progression rate in patients with chronic hepatitis C (CHC). Two hundred seventy consecutive untreated patients with CHC of known duration undergoing liver biopsy were studied. Demographic, epidemiological, metabolic, and virological data were recorded, and detailed histories of cannabis, alcohol, and tobacco use over the span of hepatitis
C virus infection were obtained. Fibrosis stage, steatosis, and activity grades were scored according to Metavir system. Patients were categorized as noncannabis users (52.2%), occasional users (14.8%), or daily users (33.0%), and the relationship between cannabis use and fibrosis progression rate (FPR) or fibrosis stage was assessed. On multivariate analysis, six factors were independently related to a FPR greater than 0.074 (median value of the cohort): daily cannabis use (OR = 3.4 [1.5-7.4]), Metavir activity grade A2 or higher (OR = 5.4 [2.9-10.3]), age at contamination of more than 40 years (OR = 10.5 [3.0-37.1]), genotype 3 (OR = 3.4 [1.5-7.7]), excessive alcohol intake (OR = 2.2 [1.1-4.5]), and steatosis (OR = 2.0 [1.0-4.1]). Daily cannabis use was also an independent predictor of a rapid FPR (>0.15) (OR = 3.6 [1.5-7.5]). Finally, severe fibrosis (≥F3) was also predicted by daily cannabis use (OR = 2.5 [1.1-5.6]; P = .034), independently of Metavir activity grade, excessive alcohol intake, age at liver biopsy, steatosis, and tobacco smoking. In conclusion, daily cannabis smoking is significantly associated with fibrosis progression during CHC. Patients with ongoing CHC should be advised to refrain from regular cannabis use.


The current failure of potent immunosuppressive agents to control progressive disease in multiple sclerosis has moved a focus from immunotherapy towards the need for neuroprotection. There is increasing evidence for cannabinoid-mediated control of symptoms, which is being more supported by the underlying biology. However there is accumulating evidence in vitro and in vivo to support the hypothesis that the cannabinoid system can limit the neurodegenerative possesses that drive progressive disease, and may provide a new avenue for disease control.


Abstract: Objective: To determine the prevalence of self-reported substance use during pregnancy in South Australia, the characteristics of substance users, their obstetric outcomes and the perinatal outcomes of their babies. Methods: Multivariable logistic regression with STATA statistical software was undertaken using the South Australian perinatal data collection 1998-2002. An audit was conducted on every fifth case coded as substance use to identify the actual substances used. Results: Substance use was reported by women in 707 of 89 080 confinements (0.8%). Marijuana (38.9%), methadone (29.9%), amphetamines (14.6%) and heroin (12.5%) were most commonly reported, with polydrug use among 18.8% of the women audited. Substance users were more likely than non-users to be smokers, to have a psychiatric condition, to be single, indigenous, of lower socio-economic status and living in the metropolitan area. The outcome models had poor predictive powers. Substance use was associated with increased risks for placental abruption (OR 2.53) and antepartum haemorrhage from other causes (OR 1.41). The exposed babies had increased risks for preterm birth (OR 2.63), small for gestational age (OR 1.79), congenital abnormalities (1.52), nursery stays longer than 7 days (OR 4.07), stillbirth (OR 2.54) and neonatal death (OR 2.92). Conclusions: Substance use in pregnancy is associated with increased risks for antepartum haemorrhage and poor perinatal outcomes. However, only a small amount of the variance in outcomes can be explained by the substance use alone. Recent initiatives to improve identification and support of women exposed to adverse health, psychosocial and lifestyle factors will need evaluation.


In the nineteenth century, marijuana was prescribed by physicians for maladies ranging from eating disorders to rabies. However, as newer, more effective drugs were discovered and as the potential for abuse of marijuana was recognized, its use as a therapeutic became restricted, and only recently has its therapeutic potential been re-evaluated. Recent studies in animal models and in humans have produced promising results for the treatment of various disorders.
such as obesity, cancer, and spasticity and tremor due to neuropathology - with drugs based on marijuana-derived cannabinoids. Moreover, as I discuss here, a wealth of information also indicates that these drugs have immunosuppressive and anti-inflammatory properties; therefore, on the basis of this mode of action, the therapeutic usefulness of these drugs in chronic inflammatory diseases is now being reassessed.


ABSTRACT As the current antipsoriatic medications are commonly associated with deleterious side-effects, a determined search for safer agents, which could be used alone or in combination with current antipsoriatic drugs, would be very imperative. Psoriasis is believed to be characterized by a type 1 cytokine pattern; interferon-gamma, interleukin (IL)-2 and tumour necrosis factor (TNF)-alpha are predominantly expressed in this disorder. Nitric oxide, reactive oxygen species, histamine, leukotriene B(4), and increased keratinocyte cyclic adenosine monophosphate/cyclic guanosine monophosphate (cAMP/cGMP) ratio are supposed to play roles in the pathogenesis of this disorder. Based on the immunopathogenesis of psoriasis, this paper introduces three novel, potential treatments for this clinical conundrum: (i) cannabinoids, which exert inhibitory effects on antigen processing and macrophage/T-cell interaction and also on the release of IL-2, TNF-alpha and nitric oxide from immune cells; (ii) loratadine, which is an antihistamine capable of decreasing the cAMP/cGMP ratio and the production of leukotriene B(4); and (iii) allopurinol, which scavenges free radicals, inhibits the production of TNF-alpha, and downregulates the expression of intercellular adhesion molecule-1 and P2X(7) receptors on monocytes/macrophages, which are involved in antigen presentation and production of the inflammatory response, respectively. Importantly, allopurinol, especially in combination with cyclosporin, has been shown to be effective against experimental autoimmune uveitis, which, like psoriasis, is a cell-mediated autoimmune disorder.


A 19-year-old patient had developed a depersonalisation disorder following the use of considerable amounts of cannabis for several weeks two years before. The symptoms decreased sharply after treatment with a serotonergic antidepressant. In cases of persistent or recurrent symptoms of depersonalisation, both psychiatric and somatic causes should be looked for. In cases of primary depersonalisation, the use of (soft) drugs should be considered in the differential diagnosis. Various forms of pharmaco- and psychotherapy seem to be able to reduce the symptoms. However, the effectiveness of no treatment has yet been proven.


Use of cannabis as a medicine for numerous conditions has a well-documented history stretching back thousands of years. With the identification of an endogenous system of receptors and ligands in recent years, abundant experimental data have reinforced the anecdotal claims of people who perceive medicinal benefit from the currently illegal consumption of cannabis. This, combined with data from recent clinical trials, points to the prospect of cannabis as a medication in the treatment of multiple sclerosis and numerous other medical conditions.


Preclinical findings on ajulemic acid (AJA) showed analgesic and anti-allodynic effects without psychoactive properties making it an appealing substance for the treatment of pain. A recently published randomized double-blind crossover clinical trial described the pain-reducing effects and side effect profile of AJA on 21 patients with chronic neuropathic pain. In this report from this same sample the effects of AJA on the mechanical hypersensitivity, on pain, and on
psychological and physical performance were further characterized. During a 5-week study period, patients were divided into two 7-day treatment groups receiving either AJA or placebo capsules first, respectively. All patients received 40 and 80mg of AJA or placebo daily in each treatment period. Pain measurements included the determination of mechanical hypersensitivity using the von Frey hair method as well as the visual analog scale (VAS), for which the number needed to treat (NNT) was calculated. The side effect profile of the compound was evaluated using psychotropic and physical measurements as well as obtaining reports on possible subjective side effects. The results showed no significant reduction in mechanical hypersensitivity (p=0.052), although a tendency towards pain reduction could be seen. The VAS score showed significant pain reduction (p=0.021) and NNT values for 30% pain relief were 2.14 for the first treatment group and 5.29 for the second treatment group. No significant findings were observed regarding psychotropic or physical measurements. Reported subjective side effects were mainly dry mouth, tiredness and dizziness and did not increase with dose elevation. Overall, these study findings indicate that AJA shows pain-reducing effects on patients with chronic neuropathic pain without clinically relevant psychotropic or physical side effects.


Various lines of evidence suggest an association between cannabis and psychosis. Five years ago, the only significant case-control study addressing this question was the Swedish Conscript Cohort. Within the last few years, other studies have emerged, allowing the evidence for cannabis as a risk factor to be more systematically reviewed and assessed. Using specific search criteria on Embase, PsychINFO and Medline, all studies examining cannabis as an independent risk factor for schizophrenia, psychosis or psychotic symptoms, published between January 1966 and January 2004, were examined. Additional studies were also reviewed from references found in retrieved articles, reviews, and a cited reference search (ISI-Web of Science). Studies selected for meta-analysis included: (i) case-control studies where exposure to cannabis preceded the onset of schizophrenia or schizophrenia-like psychosis and (ii) cohort studies of healthy individuals recruited before the median age of illness onset, with cannabis exposure determined prospectively and blind to eventual diagnosis. Studies of psychotic symptoms were also tabulated for further discussion. Eleven studies were identified examining the relationship between cannabis use and psychosis. Seven were included in the meta-analysis, with a derived odds ratio (fixed effects) of 2-9 (95% confidence interval = 2.4-3.6). No evidence of publication bias or heterogeneity was found. Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia. In conclusion, the available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.


No abstract.


The use of cannabis for medical purposes is a controversial but an important topic of public and scientific interest. We report on the results of a self-administered questionnaire study conducted in the United Kingdom between 1998 and 2002. The questionnaire consisted of 34 items and included demographic data, disease and medication use patterns and cannabis use profiles. Subjects were self-selected; 3663 questionnaires were distributed and 2969 were returned [1805 (60.9%) women, mean age 52.7 years (SD 12.7)]. Medicinal cannabis use was reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%). Medicinal cannabis use was associated with younger age,
male gender and previous recreational use (p < 0.001). While caution must be exercised in interpreting these data, they point to the need for clinical studies of cannabis and cannabinoids with standardised and quality-controlled products.


Despite the major benefits of antiretroviral therapy on survival during HIV infection, there is an increasing need to manage symptoms and side effects during long-term drug therapy. Cannabis has been reported anecdotally as being beneficial for a number of common symptoms and complications in HIV infections, for example, poor appetite and neuropathy. This study aimed to investigate symptom management with cannabis. Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. Symptom control using cannabis is widespread in HIV outpatients. A large number of patients reported that cannabis improved symptom control.

**BEHAVIOURAL SCIENCE**


The purpose of this study was to examine the relationship between psychological distress, self-efficacy, and marijuana use using data from a randomized controlled trial of treatments for marijuana dependence [J. Consult. Clin. Psychol. 68 (2000) 898-908]. Adult marijuana users seeking treatment (N=291) were randomly assigned to three treatment conditions: (1) cognitive-behavioral relapse prevention support group (RPSG), (2) individualized assessment and advice group (IAI), and (3) delayed treatment control group (DTC). As predicted, psychologically distressed individuals had lower self-efficacy for avoiding marijuana use in psychologically distressing (PD) situations as opposed to nonpsychologically distressing (NPD) situations. However, all participants tended to have lower self-efficacy for NPD situations than PD situations. Efficacy increased and marijuana use decreased following treatment but the RPSG treatment did not have greater benefit for psychologically distressed participants.


Despite the fact that rates of cannabis dependence have increased substantially over the past several years, there are no medications approved for the treatment of cannabis dependence. This paper reviews data from recent research on cannabinoids that may be relevant for the development of pharmacotherapies for cannabis dependence. Included in the discussion are findings from studies that have assessed the ability of medications to ameliorate cannabis-related abstinence symptoms in laboratory animals and human research participants. Data from studies that have investigated the effects of pharmacological agents on cannabis self-administration are also reviewed because these data may provide information critical for informing relapse prevention medication development efforts. The majority of published studies evaluating cannabis pharmacotherapies have focused on decreasing withdrawal symptoms: a growing number of medications reduce symptoms in laboratory animals, but the majority of these medications have not been tested in humans. Fewer studies have assessed the effects of potential cannabis treatment medications on cannabinoid-related reinforcing effects. In laboratory animals, only the CB1 cannabinoid antagonist rimonabant has shown promise. In humans, this medication has not been tested on cannabis reinforcing effects. To date, no medication has been shown to alter cannabis self-administration by humans.

OBJECTIVE: To describe an innovative treatment for adolescent marijuana abuse and provide initial information about its feasibility, acceptability, and potential efficacy. METHOD: Provided an intervention composed of (1) a clinic-administered, abstinence-based incentive program; (2) parent-directed contingency management targeting substance use and conduct problems; (3) a clinic-administered incentive program for parent participation; and (4) individual cognitive-behavioral therapy for adolescents. Data are presented for 19 adolescents, age 15-18 years. Measures of substance use, psychopathology, and parenting were collected before and after the 14-week treatment. Substance use measures were also collected 1 month post-treatment. Substance use was monitored by twice-weekly urine and breath testing. An intent-to-treat model was used. RESULTS: Adolescents and parents attended an average of 10.3 and 10.6 of 14 sessions, respectively. Substance use, externalizing behaviors, and negative parenting behaviors decreased by treatment end. Urine testing indicated that abstinence increased from 37% at intake to 74% at treatment end (z value = 2.28, p = .02) and that 53% of adolescents were abstinent 30 days post-treatment. CONCLUSIONS: Preliminary data provide support for the feasibility and acceptability of a family-based, contingency management model to treat adolescent substance use and conduct problems. Controlled efficacy studies with larger samples are needed.


BACKGROUND: Cannabis consumption among teenagers has undergone dramatic changes in Europe since the beginning of the 1990s. A number of behaviors associated with cannabis consumption, such as tobacco smoking, excessive drinking and truancy are developing too, each in their own way. METHODS: To assess the evolution over time of the various types of cannabis consumption (both ever and weekly consumption) in relation to these determinants (age, sex, studies chosen, truancy, tobacco smoking and recurrent intoxication), we have analyzed the cross-sectional study on Health Behaviour in School-Aged Children in the French-speaking Belgian Community (12-17 years) since 1994. We used logistic models to analyze the evolution of the various types of cannabis consumption and to identify the associated factors. Finally, in order to demonstrate time trends, we tested for each type of consumption in the interactions between the significant predictive variables in each model and the survey year (1994-1998-2000). RESULTS: Rates of ever use, past 30-day use and weekly use among the ever users have been increasing from 1994 to 2002 and reached, respectively, 22.0%, 11.6%, 6.8% and 32.9%. Cannabis ever use rose more noticeably among the general education students (adjusted OR (95%CI)): 3.08 (2.66-3.57) and among the truants: 4.57 (3.39-6.14). Weekly cannabis smoking rose most especially among the truants: 1.92 (1.34-2.78). CONCLUSION: Truants should constitute a priority target for the prevention of cannabis consumption, while the phenomenon of truancy must be moreover examined in depth in order to more thoroughly identify the appropriate prevention programs organized both in and outside of the school environment.


According to the 'acquired preparedness model,' expectancies mediate the relationship between an impulsive personality style and alcohol use. The current study evaluated whether the model can also be applied to marijuana use. Estimated probabilities and subjective evaluations of personally expected marijuana effects, along with impulsivity and frequency of marijuana use, were assessed in 337 college undergraduates. Tests of mediation examining positive and negative marijuana expectancies showed negative expectancies to be a significant mediator for both males and females. That is, participants who were higher on impulsivity had fewer negative expectancies and in turn used more marijuana. This study provides evidence that the acquired preparedness model may help to explain marijuana use.

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